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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 :		(11) International Publication Number: WO 84/ 04453
A61K 7/16	A1	(43) International Publication Date: 22 November 1984 (22.11.84)

(21) International Application Number: PCT/SE84/00191

(22) International Filing Date: 18 May 1984 (18.05.84)

(31) Priority Application Number: 8302789-6

(32) Priority Date: 18 May 1983 (18.05.83)

(33) Priority Country: SE

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(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: ORAL DENTAL CARE COMPOSITION

(57) Abstract

An oral dental care composition for inhibiting or preventing periodontoclasia and caries containing special sulfated polysaccharides, viz. xylan sulfate, dextran sulfate, starch sulfate or hyaluronic acid sulfate, in combination with a non-toxic carrier. The composition may e.g. have the form of a tooth cleaning agent, a suction or chewing tablet, a chewing gum, a rinsing solution or a solid or liquid concentrate intended to form a rinsing solution by dissolution or dispersion or suspension in water or another liquid or liquid mixture. Claimed is further the use of these sulfated polysaccharides as anti-periodontoclasia or anti-caries agents for oral administration.

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Oral Dental Care Composition

Technical Field

The present invention relates to oral dental care compositions containing special sulfated polysaccharides which inhibit the enzymatic degradation of collagen. It also relates to the use of these sulfated polysaccharides as anti-periodontoclasia agents (anti-tooth loosening agents).

Background of the Invention

Caries is a well known and wide spread tooth disease which affects people in all ages and which causes great economical losses both to the patient and the society, not to speak of the accompanying physical and mental suffering for the patient. Caries is caused i.a. by acid attacks on the hepatite layer of the tooth enamel exposing the tooth dentin, which is more easily subjected to bacterial growth than the enamel. The mouth-cavity with its environment is an excellent place of growth for various bacteria, and the dentin is also a good breeding ground for bacterial growth.

Many attempts have been made to develop agents which inhibit the formation of caries and/or inhibit the development of already existing caries. Many of the prior proposals for solving the caries problems are directed to improving the acid resistance of the tooth enamel and the dentin, and to this end e.g. anti-caries agents containing certain tin compounds have been used. It has also e.g. been proposed to use anti-caries agents containing fluorine ions together with tin ions, whereby, in addition to improved acid resistance, inhibition of caries because the teeth have absorbed the fluorine has been achieved.

The published European patent application 0083486 discloses anti-caries compositions containing certain low molecular thiol and disulfide compounds, having collagenase-inhibiting activity. Because these compounds are low molecular they can be resorbed and certain toxicity problems can be expected when used as an oral dental care agent, wherein it is inherent in the nature of the treatment that the treated person may swallow comparatively great amounts of the compounds in question. Further, many low molecular thiols and disulfides have unpleasent smell and taste which can be difficult to hide. Furthermore, these prior art compositions are only intended for use as anti-caries agents, but there is no disclosure of any use thereof as anti-periodontoclasia agents.

Although these and other prior art anti-caries agents have given certain positive results, there is still a great need for alternative or improved anti-caries agents.

Tooth loosening - or parodental diseases - is i.a. caused by destruction of the tissue surrounding the necks of the teeth and of the parodental membranes, i.e. the fine filaments by means of which the teeth are suspended in the alveols.

As far as we know, no anti-periodontoclasia agents are known, despite the fact that such agents would meet a very great demand.

Object of the Invention

The present invention aims at providing improved oral dental care compositions which inhibit or prevent the formation and/or development of tooth-loosening and caries.

The invention is based on an approach which is somewhat similar to that of the above mentioned European patent application 0083486, viz. starting from the realization that certain bacteria, which are present in the mouth-cavity and on the teeth, form collagen-degrading enzymes, such as collagenase, elastase, etc. and that the presence of these enzymes play an important role for the formation and development of tooth-loosening and caries. In caries this effect is assumed to be related to the fact that these enzymes, when the collagen-rich dentin has been exposed by acid attack on the enamel, rapidly degrades the collagen structure of the dentin, whereby the apatite loses its coupling with the collagen and therefore can be easily dissolved. In an analogeous manner tooth-loosening is assumed to be caused by the fact that these enzymes degrade the collagen filaments keeping the tooth attached to the tooth bone. It should, however, be underlined that this description of the assumed mechanism is not in any way intended to limit the invention.

Brief Description of the Invention

The basic idea of the invention is to block or inhibit the collagen-degrading enzymes formed in the mouth-cavity and on the teeth, so that they become inactive and consequently lose the ability to enzymatically degrade the root and tooth collagen. To this end the dental care agents according to the invention contain special sulfated polysaccharides which are non-toxic on oral administration and which preferably have a neutral or comparatively pleasant taste. These sulfated polysaccharides form a group of compounds which is known as such.

The sulfated polysaccharides used according to the invention are xylan sulfate, dextran sulfate, starch sulfate and hyaluronic acid sulfate. In contrast to the low molecular thiol and disulfide compounds disclosed in the above mentioned European patent application 0083486, these sulfated polysaccharides have relatively high molecular weights, are completely non-toxic, and are not absorbed by the body even on considerable use in oral dental care compositions. Especially three first-mentioned sulfated polysaccharides, which are the preferred ones, are cheap and readily available substances, which is a great advantage. They also exhibit a surprisingly good and extended effect, especially against tooth-loosening, which is assumed to result from a (more or less specific)

binding to the mucous membranes in the mouth, e.g. in a tooth pocket between the teeth. The binding probably occurs with the sulfate groups turned outwards, whereby they are not inactivated by the binding. This capability of binding to the mucous membranes in the mouth probably depends on the special ring structure of the sulfated polysaccharides.

The oral dental care compositions according to the invention may, in addition to the indicated sulfated polysaccharides and conventional inert carriers and/or diluents suitable for oral administration, also contain one or more other active dental care substances, provided that the same do not detrimentally affect the capability of the sulfated polysaccharides to inhibit collagen degradation. These inert carriers/diluents and other active dental care substances respectively are, of course, chosen with regard to the special form of preparation and the intended method of use.

In another aspect the invention relates to the use of the above indicated sulfated polysaccharides as anti-periodontoclasia agents and anti-caries agents.

Description of Preferred Embodiments

The sulfated polysaccharides which are especially preferred for use according to the invention are xylan sulfate, dextran sulfate, and starch sulfate. They are substantially non-toxic on oral administration in doses which inhibit the degrading of collagen, and they have a neutral or pleasant taste. The sulfated polysaccharides can be of any suitable molecular weight, but they preferably have a molecular weight in the interval about 2000-50,000, especially about 2000-20,000. As examples can be mentioned dextran sulfate of a molecular weight of about 2000-20,000, hyaluronic acid sulfate of a molecular weight of about 2000-50,000, starch sulfate of a molecular weight of about 2000-20,000, and xylan sulfate of a molecular weight of about 2000-15,000. As used herein the term "sulfated polysaccharides" also includes non-toxic salts, e.g. with such cations as metall ions (e.g. alkali metal, especially sodium salts), ammonium ions, and with organic bases such as amines.

The sulfated polysaccharides used according to the invention, which for simplicity reasons will be called collagenase-inhibitors below, can be incorporated into oral compositions by means of methods and means which are known as such, the formula of the composition, including the content of collagenase-inhibitor and the form of preparation, naturally being adapted to the intended method of use. The collagenase-hinibitors can, e.g., be incorporated into tooth cleaning agents such as tooth paste, chewing gum or chewing tablets, mouth rinsing agents such as rinsing solutions, tablets or powders which are soluble in water or can be slurred in water, and the like.

These oral preparations may contain well known inert adjuvants and/or

other dental care agents. For example, tooth paste may contain suitable abrasives (such as silica), binders (such as hydroxy ethyl cellulose), etc. Rinsing tablets and powders, which are intended to be mixed with or dissolved/dispersed in e.g. water on use, can e.g. be prepared well known manner by means of well known vehicles (such as lactose and mannitol), binders (such as corn starch), etc. Chewing gums, suction or chewing tablets and the like may contain ingredients which are conventional for such products. The oral compositions according to the invention may further contain e.g. sweeteners, taste improving agents, preservatives, thickeners, etc.

The amount of collagenase-inhibitor in the oral compositions according to the invention varies with regard to the chosen form of preparation, the specific collagenase-inhibitor used, the intended frequency of administration, the effect aimed at, etc. Very good results are achieved already at very low doses, e.g. of the order of 10 µg per 10 ml of a prepared rinsing solution, which is given 1 to 3 times daily with a rinsing time of one or a few minutes each time. This dosage can serve as a guideline for the dosage in the other forms of preparations, but it is not to be construed as any limitation of the invention, which is intended to comprise all dose levels giving the effect aimed at. The frequency of treatment normally ought to be at least once daily.

The inhibiting effect on tooth-loosening and caries when using the collagenase inhibitors according to the invention has been shown by the following test, in which teeth extracted from one and the same patient were used. Comparable teeth were paired in groups of two. An attack of caries was triggered by means of a collagenase solution containing about 3 mg collagenase per ml water. As a control that the collagenase activity of the solution did not diminish with time, one drop of the solution was dropped onto a sheet of collagen every hour. A maintained collagenase activity was observed during the entire test period by the ability of the solution to make a hole of drop size in the collagen sheet. As a model for demonstrating anti-tooth-loosening effect (Test 3) corresponding tests were carried out on extracted teeth having substantially intact collagen filaments and root cement.

5 mg of the preferred sulfated polysaccharide, viz. xylan sulfate, in 5 ml water was used as test solution.

Test 1: Two first premolars from the same mouth and with substantially uneffected enamel layer were kept immersed in collagenase solution for 8 hours with and without (control) addition (5 ml) of the test solution. The teeth were examined with the naked eye, under microscope and mechanically with a spatula both before and after the test. The enamel layer of both teeth was substantially unchanged after the test, but a clear attack of caries on the control tooth was

observed at the transition to the root. The test tooth was intact also in this area.

Test 2: On two first premolars from the same mouth similar enamel damages were created mechanically. The same control and test solutions were used as in Test 1. One drop of each solution was applied to the respective enamel damage. On examination (with the naked eye, under microscope and by means of a spatula) after 8 hours the enamel damage was found to be unchanged on the test tooth, whereas the control tooth showed clear signs of beginning caries (discolouration, rough surface).

Test 3: Two comparable premalars from the same mouth, having comparatively unaffected root cement and unaffected collagen filaments, were kept immersed in a collagenase solution for 4 hours. The test tooth had been pretreated by immersion in the above test solution (xylan sulfate) for 30 minutes. No pretreatment of the test tooth. After termination of the immersion in the collagenase solution the teeth were examined under microscope. In the test tooth both the root cement and the collagen filaments were unaffected. In contrast both the root cement and the collagen filaments had been destroyed in the control tooth.

CLAIMS

1. An oral anti-tooth loosening and anti-caries composition, characterized in that it comprises a non-toxic, collagen degradation inhibiting amount of at least one sulfated polysaccharide selected from the group consisting of xylan sulfate, dextran sulfate, starch sulfate, and hyaluronic acid sulfate, in combination with a non-toxic carrier.

2. The composition according to claim 1, characterized in that it is in the form of a tooth cleaning agent, a suction or chewing tablet, a chewing gum, a rinsing solution or a solid or liquid concentrate intended to form a rinsing solution by dissolution, dispersion or suspension in water or another liquid or liquid mixture.

3. The composition according to claim 1 or 2, characterized in that the sulfated polysaccharide has a molecular weight in the interval about 2000-50,000, preferably about 2000-20,000.

4. The composition according to any one of claims 1 to 3, characterized in that the sulfated polysaccharide is selected among xylan sulfate, dextran sulfate and starch sulfate.

5. Use of xylan sulfate, dextran sulfate, starch sulfate or hyaluronic acid sulfate as anti-tooth-loosening agents for oral administration.

6. Use of xylan sulfate, dextran sulfate, starch sulfate or hyaluronic acid sulfate as anti-caries agents for oral administartion.

7. Use according to claim 5 or 6, characterized in that the sulfated polysaccharide has a molecular weight in the interval about 2000-50,000, especially about 2000-20,000.

8. Use according to claim 5 or 6, characterized in that the sulfated polysaccharide is dextran sulfate, starch sulfate or xylan sulfate.

9. A method of inhibiting or preventing tooth-loosening, characterized by orally administering a periodontoclasia-inhibiting amount of at least one sulfated polysaccharide selected from the group consisting of xylan sulfate, dextran sulfate, starch sulfate, and hyaluronic acid sulfate, to a patient in need thereof.

10. A method of inhibiting or preventing caries, characterized by orally administering a caries-inhibiting amount of at least

one sulfated polysaccharide selected from the gorup consisting of xylan sulfate, dextran sulfate, starch sulfate, and hyaluronic acid sulfate, to a patent in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE84/00191

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC 3

A 61 K 7/16

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC 1	A 61 K 7/16; C 08 B 19/02
IPC 2+3	A 61 K 7/16; C 08 B 31/06, 37/00, 37/02, 37/08
US Cl	426: 49, 56; 536: 107, 112, 118, 122

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	GB, A, 1 335 564 (MARINE COLLOIDS INC) 31 October 1973, page 3, lines 79-86 and page 9.	1-4
Y	Chemical Abstracts, Vol 93 (1980), abstract No 19496h, Cas.Lek.Cesk. 1977, 116(28), 869-73 (Slo).	1-8
Y,P	EP, A2, 0 083 486 (BINDERMAN I & MECHANIC GL) 13 July 1983	1-2
Y	GB, A, 1 284 728 (ASPRO-NICHOLAS LIMITED) 9 August 1972, page 1, lines 27-54.	1-8
A	FR, A, 2 036 453 (HENRY M) 24 December 1970	1-8

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [3]
1984-08-03	1984 -08- 10
International Searching Authority [1]	**Signature of Authorized Officer [20]**
Swedish Patent Office	Margareta Danielsson Margareta Danielsson

K.L.

Form PCT/ISA/210 (second sheet) (October 1981)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 9-10, because they relate to subject matter [12] not required to be searched by this Authority, namely:

methods for therapeutical treatment of the human or animal body.

2. [ ] Claim numbers ....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out [13], specifically:

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.
2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.